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ARTICLE

Evaluation of postprandial total triglycerides within the TIGG model for characterizing postprandial response of glucose, insulin, and GLP-1

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Abstract

The TIGG model is the first model to integrate glucose and insulin regulation, incretin effect, and triglyceride (TG) response in the lipoprotein subclasses of chylomicrons and VLDL-V6. This model described the response following a high-fat meal in individuals who are lean, obese, and very obese and provided insights into the possible regulation of glucose homeostasis in the extended period following a meal. Often, total TGs are analyzed within clinical studies, instead of lipoprotein subclasses. We extended the existing TIGG model to capture the observed total TGs and determined if this model could be used to predict the postprandial TG response of chylomicron and VLDL-V6 when only total TGs are available. To assess if the lipoprotein distinction was important for the model, a second model (tTIGG) was developed using only the postprandial response in total TGs, instead of postprandial TG response in chylomicrons and VLDL-V6. The two models were compared on their predictability to characterize the postprandial response of glucose, insulin, and active GLP-1. Both models were able to characterize the postprandial TG response in individuals who are lean, obese, or very obese following a high-fat meal. The extended TIGG model resulted in a better model fit of the glucose data compared to the tTIGG model, indicating that chylomicron and VLDL-V6 provided additional information compared to total TGs. Furthermore, the expanded TIGG model was able to predict the postprandial TG response of chylomicrons and VLDL-V6 using the total TGs and could therefore be used in studies where only total TGs were collected.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The interplay between glucose and triglycerides (TGs) has been characterized. Many studies collect total TGs do not differentiate lipoprotein subclasses, the exogenous, and the endogenous pathways.

WHAT QUESTION DID THIS STUDY ADDRESS?

We quantitively characterized the postprandial response of glucose, insulin, active GLP-1, and TGs following a high-fat meal in individuals who are lean, obese, and very obese. We assessed the importance of the lipoprotein subclasses for characterizing postprandial response during an extended period after a high-fat meal.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The extended TIGG model resulted in a better model fit of the glucose data compared to the tTIGG model, indicating that chylomicrons and VLDL-V6 provided additional information compared to total TGs.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

These findings would be of significant interest to those studying metabolism, especially in relation to pharmacological interventions against obesity and diabetes. The expanded TIGG model was able to predict the postprandial response of chylomicrons and VLDL-V6 from total TGs.

INTRODUCTION

Mathematical models are powerful tools to aid in understanding complex relationships within biology. The application of models within the field of diabetes is well-established and has contributed largely to the increased understanding of the complex interplay between glucose and insulin. The integrated glucose-insulin model is a semimechanistic model that describes the glucose homeostasis[1] and it has been used to support clinical drug development.[2–4] Recently, this model was improved by adding other major regulators of metabolism, such as lipids and incretins. The triglyceride-insulin-glucose-GLP-1 (TIGG) model integrated glucose and insulin regulation, incretin effect, along with the triglyceride (TG) response in the lipoprotein subclasses of chylomicrons and VLDL-V6 in a semimechanistic way.[5] This model described the postprandial response following a high-fat meal in individuals who are lean, obese, and very obese and provided insight into the differential regulation of glucose homeostasis between lean and obese individuals in the extended period after a meal.[5]

The use of mixed meal tolerance or lipid tolerance test to support clinical drug development has increased over the years with the growing understanding of the complex relationship of other nutrients beyond just the glucose/insulin response. However, many studies still collect total TG to assess the postprandial response. Total TGs do not differentiate between the exogenous (chylomicrons via the gut) and the endogenous pathways (VLDL via secretion from the liver) in the body which is provided in the lipoprotein subclasses. Importantly, we have shown that the postprandial TG response of VLDL-V6 differed between individuals who are lean and individuals who are obese.[6] Similarly, others have found that most of the postprandial TG response is represented in VLDL,[7] and larger VLDL may be more influential in metabolic syndrome,[8] insulin resistance, obesity, and weight regulation. Lipoprotein subclass of TGs provides a better understanding of physiology.

Collecting samples for lipoprotein analysis compared to total TG analysis can be more challenging. Sample handling steps, including sample collection, preparation, analysis, and storage, are important as it can alter the lipoprotein structure.[9] Postprandial samples need to remain refrigerated to keep the integrity of the lipoprotein particles, as freezing the samples can destroy the lipoproteins.[9] Often, lipoprotein analysis requires specialized laboratories and can have shorter assay stability windows. These additional steps can result in settling for standard chemical measurements of total TGs rather than obtaining lipoprotein subclass analysis.

We sought to modify the existing TIGG model to capture the observed total TGs and determine if this model could be used to predict the postprandial TG response of chylomicron and VLDL-V6, when only total TGs data are available. To assess if the lipoprotein distinction was important for the predictions of postprandial response with an extended period after a meal, a second model (tTIGG) was developed using the postprandial response in total TGs, instead of postprandial TG response in chylomicrons and VLDL-V6. The two models were compared on their predictability to characterize the postprandial response of glucose, insulin, and active GLP-1.

METHODS

Study designs

Data for model development

Data from a previously published study were used for model development.[5,6] Sixty-four healthy individuals, 31 men and 33 women, age 26–45 years, were categorized into three populations based on their body mass index (BMI): lean (BMI of 18.5–24.9), obese (BMI of 30–33), and very obese (BMI of 34–40). Individuals were fasted overnight and received a high-fat breakfast meal containing 660 kcal, with 60% fat (~75% unsaturated/25% saturated fat), 20% protein, and 20% carbohydrates, and consumed entirely within 20 min. Blood samples were taken prior to the meal (i.e., fasting) and at 4-, 7-, 10-, and 13-h post-meal for glucose, insulin, active GLP-1, and the TGs in chylomicrons, large VLDL-V6, and total TGs.

Data for external model evaluation

Data from a previously published study were used for external model evaluation.[10] This phase I study evaluated the postprandial TG response of total TG, chylomicrons, and VLDL-V6 for 11 h after a high-fat test meal containing 1204 calories (~60% fat, 20% carbohydrates, and 20% protein) when either placebo or a single dose of LY2140112 was given to 16 overweight or obese (BMI: 27–39 kg/m^2) participants. Blood samples were taken prior to the meal (−0.5 and 0 h) and at 1, 2, 3, 4, 5, 7, 9, and 11 h post-meal. Only the placebo treatment was used for the external model evaluation.

Bioanalysis

Glucose

Plasma glucose was analyzed using a validated assay (Covance) with an interassay precision and accuracy of less than or equal to 1.1%. The lower and upper limit of quantification (LLOQ, ULOQ) was 20 mg/dL and 16,000 mg/dL, respectively.

Active GLP-1 and insulin

Plasma was collected for active GLP-1, and insulin using P100 tubes containing a cocktail of protease inhibitors, specifically optimized for stabilization of metabolic markers. Active GLP-1, and insulin were analyzed using a validated immunoassay method (Myriad RBM) with an interassay precision and accuracy of active GLP-1, and insulin of less than or equal to 12%. The LLOQ and ULOQ was 0.0281 and 140 μU/mL for insulin and 4.38 and 2200 pg/mL for active GLP-1, respectively.

Lipids

Plasma was analyzed for TG content in chylomicrons (≥170 nm), VLDL-V6 particles (VLDL-V6, 140–100 nm), and total TGs using nuclear magnetic resonance signals, broadcast by lipoprotein subclass particles of different sizes (LipoScience).[11] The TG content is reported as mg/dL (1 mg/dL = 88.5 mmol/L).

Parameter estimation and model selection

Nonlinear mixed-effect modeling was used to analyze the data, in NONMEM[12] (version VII; ICON Development Solutions) and Perl-speaks-NONMEM (PsN)[13] as the modeling environment. The first-order conditional estimation method with interaction was used. The model was implemented as ordinary differential equations using the ADVAN6 subroutine.

Selection between models was based on visual inspection of goodness-of-fit plots, including conditional weighted residuals,[14] visual predictive checks (VPCs), the objective function value (OFV), the physiological plausibility, and the precision of the parameter estimates. The likelihood ratio test was used between nested models, as the difference in OFV (provided by NONMEM) is approximately χ^2-distributed with the number of differing parameters between compared models being the degree of freedom. A p value of 0.01 was used for statistical significance. Model parameter estimates were determined along with the corresponding relative estimation error (RSE [%]). The quantified between-subject variability (BSV) was expressed as a coefficient of variation. The RSEs and 90% confidence intervals (CIs), to assess parameter precision, were calculated from a sampling importance resampling analysis, as implemented in PsN.[13] The predictive property of the model was assessed by VPCs using PsN and Xpose in R.[15] The VPC was performed with 1000 study replicates with the same design characteristics as those of the original study. At each time interval, the 10th, 50th, and 90th percentiles (i.e., 80% prediction interval [PI]) of glucose, insulin, active GLP-1, TGs in chylomicrons and VLDL-V6, and total TGs were calculated for each study replicate. The 95% CIs of these percentiles were then calculated and plotted per time interval, with percentiles calculated from the observed data overlaid. As the number of individuals

in each weight group was limited, a narrower prediction interval was investigated (i.e., 80% PI instead of 95% PI).

Model strategy

The data used for the model development for this work is the same data used for developing the published TIGG model.[5] The published TIGG submodel structures for active GLP-1, glucose, and insulin were not altered, and the model parameters were fixed, except those specified in the following bullets. Data of glucose, insulin, and active GLP-1 were retained in the models to assign empirical Bayes estimates with fixed population parameters. Two models were developed:

- The extended TIGG model, that utilized the published lipid submodel which contained the TG lipoprotein subclasses of chylomicrons and VLDL-V6, and added the contribution of all other TG subclasses to assess total TGs and,
- The tTIGG model, which replaced the published submodel containing the TG lipoprotein subclasses of chylomicrons and VLDL-V6 with a model of only total TGs.

Thus, the expanded TIGG model used chylomicrons, VLDL-V6, and total TG clinical data, whereas the tTIGG model used only the total TG clinical data. Data for chylomicrons and VLDL-V6 was retained in the expanded TIGG model to assign empirical Bayes estimates with fixed population parameters. The published lipokinetic model describes the absorption of TG from dietary fats from the gut via chylomicrons and postprandial VLDL secretion from the liver, as VLDL-V6.[5,6]

Extended TIGG model

In the extended TIGG model, the lipokinetic model structure was not altered, and all of the previous published model parameters were fixed.[5] Data from total TGs were added and modeled as the sum of dynamic chylomicron, dynamic VLDL-V6, and a constant parameter of residual TG lipoproteins subclass, pooling their contribution into one estimate.

$$\mathrm{TTG}\,(t) = \mathrm{Chylo}\,(t) + \mathrm{VLDL}\,V6\,(t) + \mathrm{LP_{res}}$$

$$\mathrm{LP_{res}} = \theta_{\mathrm{pop}} \bullet e^{\eta_i}$$

where Chylo (t) and VLDL V6 (t) are the model-derived dynamic amount of the subclasses, chylomicron and VLDL-V6, respectively. $\mathrm{LP_{res}}$ is the time-invariant amount of all other TG lipoprotein subclasses, modeled with a typical population estimate, which was estimated separately by study population, that is, θ_{Lean}, θ_{Obese}, and $\theta_{\mathrm{Very\,obese}}$ and a log-normally distributed BSV, estimated through a random variable, η belonging to a normal distribution with mean = 0 and standard deviation ω_{LPres}.

tTIGG model

A turnover model was used to model data for the total TGs, removing the models of chylomicron and VLDL-V6 from the original TIGG and assuming that the fasting total TGs collected at time = 0 represent steady-state, thus

$$\mathrm{dTTG}/\mathrm{dt} = k_{\mathrm{in}} - k_{\mathrm{out}} \bullet \mathrm{TTG}$$

$$\mathrm{TTG_{SS}} = \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}} \Longleftrightarrow k_{\mathrm{in}} = \mathrm{TTG_{SS}} \bullet k_{\mathrm{out}}$$

where k_{in} and k_{out} are the production and removal rate constants, respectively, and $\mathrm{TTG_{SS}}$ is the steady-state total TGs. This steady-state assumption for initializing the differential equation seemed appropriate as the concentration of total TGs at the end of the sampling period (13 h) was similar to the concentration at fasting.[6] As total TG concentration differed by study population, $\mathrm{TTG_{ss}}$ was estimated by study population ($\mathrm{TTG_{SS,Lean}}$, and $\mathrm{TTG_{SS,Obese/Very\,Obese}}$).

The contribution of postprandial TGs on endogenous glucose production, was applied within the model using the model-predicted, postprandial TG of total TGs. Additionally, the slope of the postprandial TG effect on endogenous glucose production (i.e., α_{G}) was estimated separately for the individuals who are lean and obese (combining both obese and very obese populations), as applied within the original TIGG model.

$$\frac{\mathrm{dGlucose}}{\mathrm{dt}} = \mathrm{EGP_{SS}} + f\,(\mathrm{TTG}) - \left(\mathrm{CL_{GI}} \bullet I_E + \mathrm{CL_G}\right) \bullet \mathrm{Glucose}$$

$$f\,(\mathrm{TG}) = \alpha_G \bullet \left(\mathrm{TTG}\,(t) - \mathrm{TTG_{SS}}\right)$$

Method evaluation and statistics

Method qualification

To compare the model-fit properties of the two models for each dependent variables separately, the empirical Bayes estimates from the model fits with all data were used to calculate the corresponding OFVs of each variable separately. The models were compared with regard to the fit of glucose, insulin, active GLP-1, and total TGs of the data used for model development. According to the Akaike Information Criterion, as no parameters were estimated and the data were the same, the model with the lowest OFV per dependent variable represented the better fit to that dependent variable.

Model predictability of the postprandial response of chylomicron and VLDL-V6

To investigate model predictability of chylomicron and VLDL-V6 from total TGs, the extended TIGG model was applied to the data from a previously published study for external model evaluation. All parameters of the extended TIGG model were fixed and only the observed data for total TG was used to re-estimate the TG model parameters (LP_{res} and $\omega_{LP\,res}$; Figure S1 presents the VPC of the total TG data). The model using these fixed parameters and only the total TG data were used to predict the postprandial dynamics of chylomicron and VLDL-V6 which was compared to the observed data. The mean concentration versus time plots for VLDL-V6 and chylomicrons were compared. Additionally, the individual incremental (or change from premeal) area under the concentration curve (iAUC) were calculated for chylomicron and VLDL-V6. Statistical comparisons were made between the observed data and the simulated data using two-sided paired *t*-tests with the assumption of normal distribution for iAUC.

RESULTS

Parameter and model evaluation

Figure 1 presents a schematic representation of the extended TIGG and tTIGG model, where the main difference is the representation of total TGs and the connection to endogenous glucose production. The equations for the models are included in Data S1. Only the parameters related to total TGs and those parameters connecting the submodel were estimated. Table 1 lists the parameter estimates of the extended TIGG model and tTIGG model and the corresponding 90% CIs. The RSEs for fixed-effects parameters were all less than 47%. The estimates of the extended TIGG model showed that the majority of the total TGs at baseline (fasting) was attributed to other TG lipoprotein subclasses than chylomicron and VLDL-V6; as they account for 88% in lean, 93% in obese, and 92% in very obese at baseline, signifying that the postprandial dynamics of total TGs was driven mainly by chylomicron and VLDL-V6. As illustrated in the VPC, both the typical profile and variability in the TG data were adequately captured in both models (Figure 2).

Comparison of model's predictability for glucose, insulin, and GLP-1

The fit of the models for glucose, insulin, active GLP-1, and total TGs separately showed that the fit for total TGs was better with the tTIGG compared to the extended TIGG model (Table 2), as expected, given that the dynamics of TG in the tTIGG model was developed using the total TG data and not the lipoprotein subclasses data. In contrast, the fit of glucose was better with the extended TIGG model compared to the

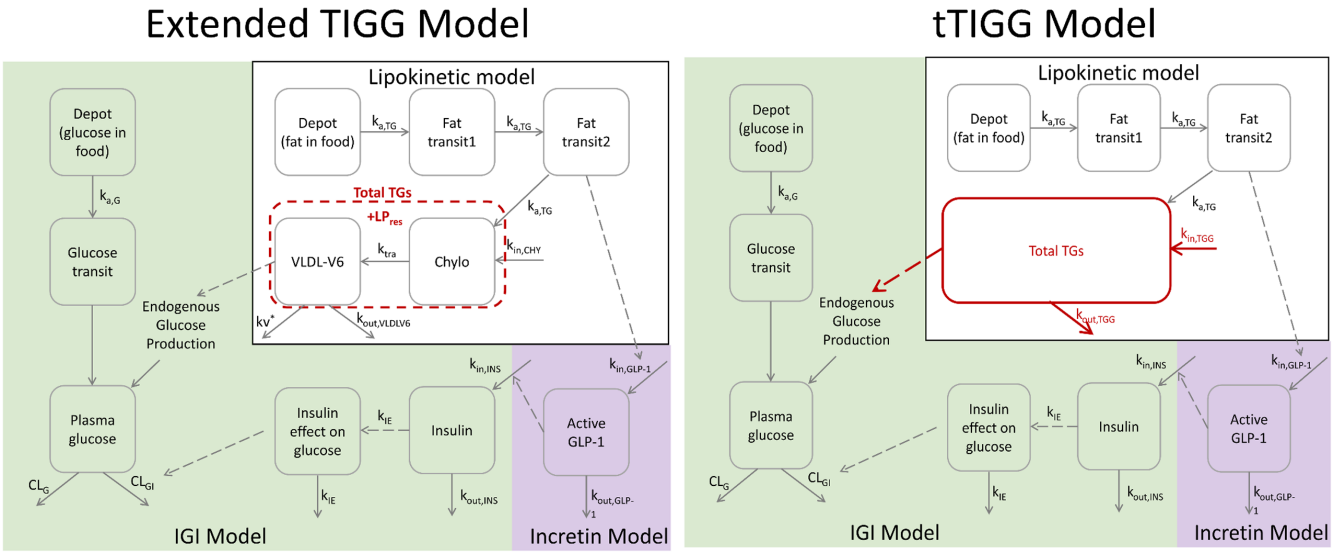

FIGURE 1 Schematic representation of the extended TIGG model (left) and tTIGG model (right). CL_G, insulin independent glucose clearance; CL_{GI}, insulin dependent glucose clearance; IGI, integrated glucose-insulin; ka_G, absorption rate constant for glucose; k_{IE}, rate constant for insulin delay; ka_{TG}, absorption rate constant for triglycerides; $k_{in,CHY}$, rate constant of production of chylomicron; $k_{in,GLP1}$, rate constant of production of active GLP-1; $k_{in,GNS}$, rate constant of production of insulin; k_{tra}, conversion rate constant for chylomicron to VLDL-V6; $k_{out,GLP1}$, first order rate constant for the elimination of active GLP1; $k_{out,INS}$, first order rate constant for the elimination of insulin;$k_{out,VLDLV6}$, first order rate constant for the elimination of VLDL-V6; *kv**, net zero order rate constant for the elimination of VLDL-V6.

TABLE 1 Final parameter estimates, typical value and BSV, with uncertainty represented as RSE and 90% CI of estimates from SIR.

Parameter description	Parameter	Unit	Typical value [RSE; 90% CI]	BSV [RSE, 90% CI]	Typical value [RSE; 90% CI]	BSV [RSE, 90% CI]
			Expanded TIGG model		tTIGG model	
Glucose-insulin system estimates						
Glucose absorption rate constant[a]	$k_{a,G}$	1/h	0.906	-	0.906	-
Insulin dependent glucose clearance[a]	CL_{GI}	L/h·mL/μU	0.497	-	0.497	-
Insulin independent glucose clearance[a]	CL_G	L/h	5.36	-	5.36	-
Volume of distribution of glucose[a]	V_G	L	9.33	-	9.33	-
Baseline glucose in lean population	$G_{Base,Lean}$	mg/dL	94.4	5.39	94.4	5.39
Baseline glucose in obese population	$G_{Base,Obese}$	mg/dL	100	5.39	100	5.39
Baseline glucose in very obese population	$G_{Base,Very\ Obese}$	mg/dL	104	5.39	104	5.39
Half-life of endogenous glucose production	$EGF_{t1/2}$	H	0.147	-	0.147	-
Elimination rate constant of insulin[a]	$k_{out,INS}$	L/h	12	-	12	-
Volume of distribution of insulin[a]	V_{INS}	L	6.09	-	6.09	-
Rate constant for insulin delay	k_{IE}	L/h	0.464	-	0.464	-
Baseline insulin in lean population	$I_{SS,Lean}$	μU/mL	0.729	69.6	0.729	69.6
Baseline insulin in obese population	$I_{SS,Obese}$	μU/mL	2.62	69.6	2.62	69.6
Baseline insulin in very obese population	$I_{SS,Very\ Obese}$	μU/mL	5.1	69.6	5.1	69.6
Slope of incretin effect	α_{INS}		0.358		0.358	
Slope of VLDL-V6 TG effect on $EGP_{SS,G}$ for lean OR slope of TG effect on $EGP_{SS,G}$ for lean	$\alpha_{G,Lean}$		10.3		70.0 [46, 46–97]	
Slope of VLDL-V6 TG effect on $EGP_{SS,G}$ for obese and very obese OR slope of TG effect on $EGP_{SS,G}$ for obese and very obese	$\alpha_{G,Obese}$		4.03		47.4 [47, 31–65]	
Residual error of glucose	RES_G	%	4.90		4.90	
Residual error of insulin	RES_{INS}	%	40.6		40.6	
Lipid system estimates						
Triglyceride absorption rate constant[a]	$k_{a,TG}$	1/h	0.606	-	0.606	-
Volume of chylomicrons and VLDL-V6 OR volume of total TGs[a]	V_{lipids}	L	8.44	-	4.0 [2.7, 4.0–4.0]	
Baseline chylomicrons[b]	CHY_{SS}	mg	28.7	29	NA	

TABLE 1 (Continued)

Parameter description	Parameter	Unit	Typical value [RSE; 90% CI]	BSV [RSE, 90% CI]	Typical value [RSE; 90% CI]	BSV [RSE, 90% CI]
			Expanded TIGG model		tTIGG model	
Transfer rate constant from chylo to VLDL-V6[a]	k_{tra}	1/h	11.6	25	NA	
Removal rate constant of VLDL-V6[a] or TGs	$k_{out,V}$	1/h	2.23	31	2.62 [29, 2.26–3.00]	51 [61, 36–66]
Baseline VLDL-V6[a]	$VLDLV6_{SS}$	mg	49	41	NA	
Effect of HOMA on k_{tra}[a,c]	EFF_{HOMA}		0.183	-	NA	
Baseline TG-lean	$LP_{res,lean}/TG_{SS,Lean}$	mg	532 [34, 450–639]	51[b]	274 [34, 227–330]	52 [45, 45–61]
Baseline TG-obese	$LP_{res,Obese}TG_{SS,Obese}$	mg	981 [32, 824–1157]	51[b]	478 [30, 416–558]	52 [45, 45–61]
Baseline TG-very obese	$LP_{res,Very\ Obese}/TG_{SS,Very\ Obese}$	mg	810 [36, 660–1001]	51[b]	478 [30, 416–558]	52 [45, 45–61]
Residual error of chylomicrons	RES_{CHO}	%	49.4		NA	
Residual error of VLDL-V6	RES_{VLDL}	%	49.2		NA	
Residual error of TG	RES_{TG}	%	30.6 [31, 23–27]		22.6 [32, 21–25]	
Incretin system estimates						
Elimination rate constant of active GLP-1	$k_{out,GLP1}$	1/h	20.8	33	20.8	33
Baseline active GLP-1	$GLP1_{SS}$	pg/mL	24.2	40	24.2	40
Slope of chylomicron effect on $k_{in,GLP-1}$	α_{GLP-1}		7.05		7.05	
Residual error of active GLP-1	RES_{GLP1}	%	21.4		21.4	

Abbreviations: BSV, between subject variability; RSE, relative estimation error; 90% CI, confidence interval; SIR, sampling importance resampling; TG, triglyceride.

[a]Parameter fixed to value reported in original publication.

[b]Estimated as one parameter for glucose and one for insulin with different typical value.

[c]$k_{tra_i} = k_{tra} \bullet \left(\frac{HOMA_i}{HOMA_{lean}}\right)^{EFF_{HOMA}} \bullet e^{\eta_i}$ where $HOMA_i$ is the individual HOMA-IR index; $HOMA_{lean}$ is the population mean of HOMA-IR index for lean population; EFF_{HOMA} is the parameter of the covariate relationship; k_{tra} is the typical value of conversion rate constant for chylomicron to VLDL-V6; η_i is individual deviation from k_{tra}; a random effect belonging to a distribution with mean zero and standard deviation ω_{ktra}.

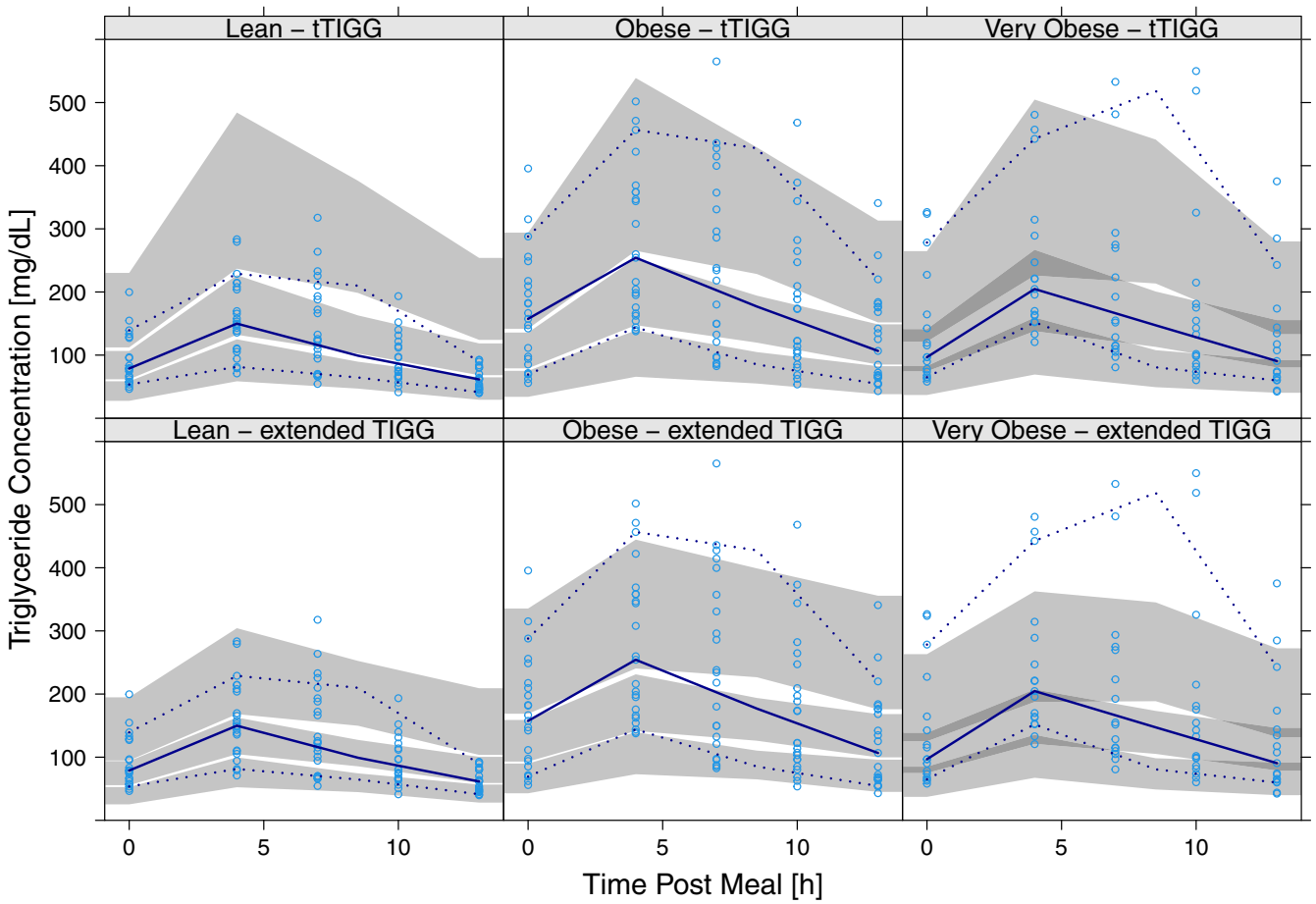

FIGURE 2 Visual predictive check of the model predictions of total triglyceride concentration for the three investigated populations: lean (left column), obese (middle column), and very obese (right column) for the extended TIGG model (bottom) and tTIGG model (top). The blue symbols are observation related: dots are observations, solid line is median, and dashed line is the 10th and 90th percentile of data. The gray shaded area represents the 95% confidence interval of the 10th, 50th, and 90th percentiles of model simulations.

TABLE 2 Comparison of model fit (i.e., objective function value) for glucose, insulin, active GLP-1 and total TGs between the extended TIGG and tTIGG models.

	Extended TIGG	tTIGG
Glucose	1499[a]	1511
Insulin	804	804
Active GLP-1	1806	1806
TG	2728	2676[a]

Abbreviation: TG, triglyceride.

[a]Indicates the better fit of the model to the data according to the Akaike Information Criterion.

tTIGG model (Table 2, Figure 3). The model fit was the same for active GLP-1 and insulin between the two models.

Model's predictability for postprandial response of chylomicron and VLDL-V6

The extended TIGG model was able to capture the overall trend of the concentration time profile of VLDL-V6 and chylomicrons (Figure 4). Additionally, a paired *t*-test showed no statistically significant differences between the observed and extended TIGG model predicted individual iAUCs of chylomicron and VLDL-V6 (mean 85 vs. 107 and 427 vs. 499 mg*h/dL; $p = 0.16$ for both). Visual inspection showed that generally the model tended to slightly overpredict the individual iAUCs compared to the observed for both lipoprotein subclasses (Figure 5). The variability of the individual chylomicron iAUCs was underpredicted; whereas the model was able to predict the variability for VLDL-V6 (Figure 5).

Covariance between baseline estimates of BSV of total TGs, chylomicron, and VLDL-V6 was introduced to potentially improve the predictive performance. This inclusion was implemented with the model development data and did not significantly improve the model. However, the covariance was retained in the model for predictions of chylomicron and VLDL-V6 with the external validation data. Model prediction with and without the covariance showed that no improvement in predictive performance was observed.

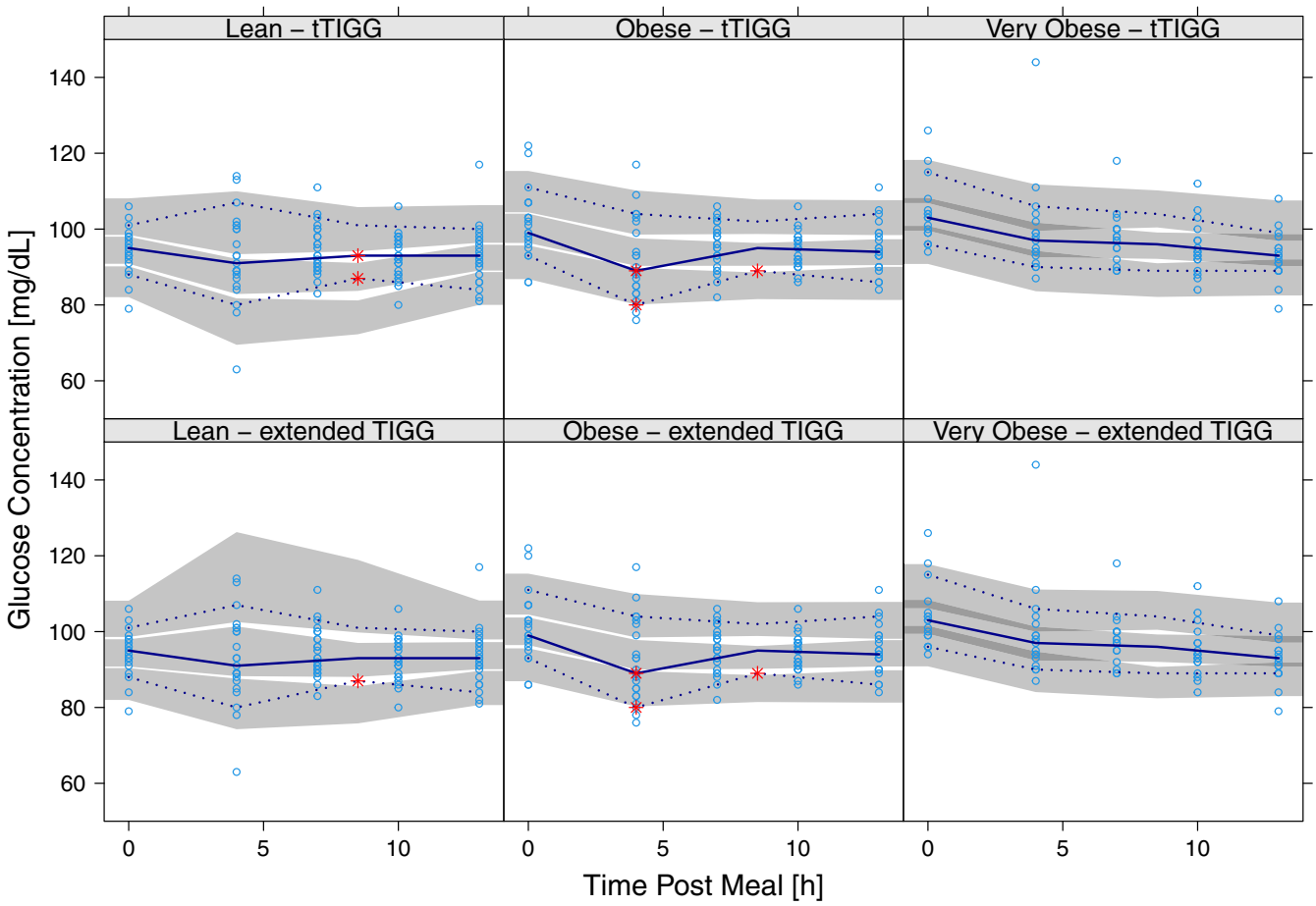

FIGURE 3 Visual predictive check of the model predictions of glucose concentration for the three investigated populations: lean (left column), obese (middle column), and very obese (right column) for the tTIGG model (bottom) and extended TIGG model (top). The blue symbols are observation related: dots are observations, solid line is median, and dashed line is the 10th and 90th percentile of data. The gray shaded area represents the 95% confidence interval of the 10th, 50th, and 90th percentiles of model simulations.

DISCUSSION

The TIGG model integrates glucose and insulin regulation, incretin effect, and postprandial TG response in chylomicrons and VLDL-V6.[5] As total triglycerides often are analyzed within clinical studies, instead of the lipoprotein TG subclasses, the TIGG model was extended by adding a baseline correction to capture the total TGs. A second model (tTIGG) was developed using only the postprandial response in total TGs, discarding chylomicrons and VLDL-V6 data. Both models were able to characterize the pre- and postprandial TG response in individuals who are lean, obese, or very obese following a high-fat meal.

To assess the importance of the lipoprotein component, the fit of the postprandial response of glucose, insulin, and active GLP-1 data was compared between the two models. The extended TIGG model provided a better model fit of the glucose compared to the tTIGG model (ΔOFV = -12), indicating the chylomicron and VLDL-V6 do provided additional information compared to total TGs. As we have previously reported, both chylomicrons and VLDL-V6 have low concentrations in the fasted state and have a prominent postprandial peak.[6] This suggests these lipoproteins' particles are primarily secreted after a high fat-meal and their TG responses are most reflective of the postprandial TG dynamics. In support of this, the extended TIGG model showed that the majority (88%–92%) of the total TGs during fasting was attributed to other TG lipoprotein subclasses than chylomicron and VLDL-V6. Importantly, the TIGG model includes a postprandial contribution of VLDL-V6 to the glucose homeostasis in the extended period after the meal. Within the tTIGG model, this relationship used total TGs, instead of VLDL-V6. As total TGs contains the VLDL-V6 response, as well as other lipoprotein subclasses, the worsened fit with the tTIGG model suggests that the other subclasses of lipoproteins confound the relationship. The same model fits were observed for insulin and active GLP-1 between the two models, as these components were conserved in the two

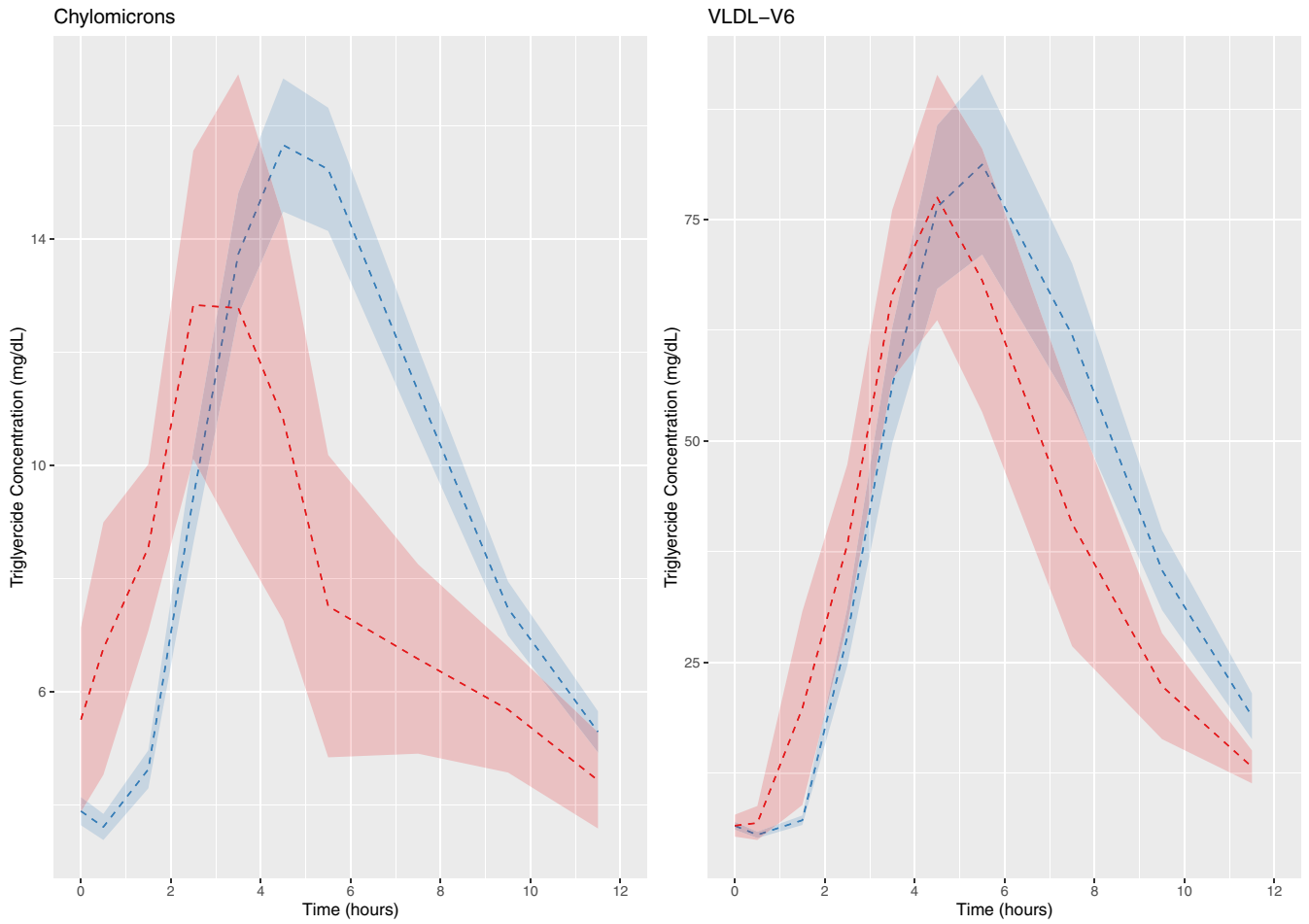

FIGURE 4 Observed (red) versus model-predicted (blue) of the mean (±SE) of TGs in chylomicron (left) and VLDL-V6 (right) where predictions originate from the extended TIGG model using only total TG data. TG, triglyceride.

models. The insulin submodel is based on the changes in active GLP-1 which were the same between the models. Although the tTIGG model uses the TG absorption from total TGs whereas the extended TIGG model uses the TG absorption from chylomicrons, it is well-established that TGs are primary transported in the intestines via chylomicrons.

Using data from a previously published study for external model validation,[5] the extended TIGG model was used to predict the postprandial TG response in chylomicrons and VLDL-V6 using the data from only total TGs with parameters of the model fixed. There was a decent prediction of the overall trend of the concentration time profile of chylomicrons and an excellent prediction of VLDL-V6, especially considering the challenges of characterizing the postprandial response of meals across studies. Additionally, these studies differed by caloric meal amount, sampling frequency, and study populations.

No statistically significant differences were identified between the observed and the predicted iAUCs of the postprandial response for either chylomicrons or VLDL-V6. There was alignment between the model-predicted and observed individual iAUC of VLDL-V6. As the dynamics of VLDL-V6 is related to glucose homeostasis within the TIGG model, this suggests the model predictions would maintain the model fidelity. Therefore, we conclude that the extended TIGG model was able to predict the postprandial TG response in chylomicrons and VLDL-V6 using the total TG data and could be used in studies where only total TGs were collected.

A limitation of this work is that it is based on relatively small clinical studies with homogeneous ethnic and racial background for each participant population. Further studies will be needed to confirm this model across various racial/ethnic backgrounds and disease states.

CONCLUSION

The extended TIGG model provided a better fit of the glucose data compared to the tTIGG model, indicating the

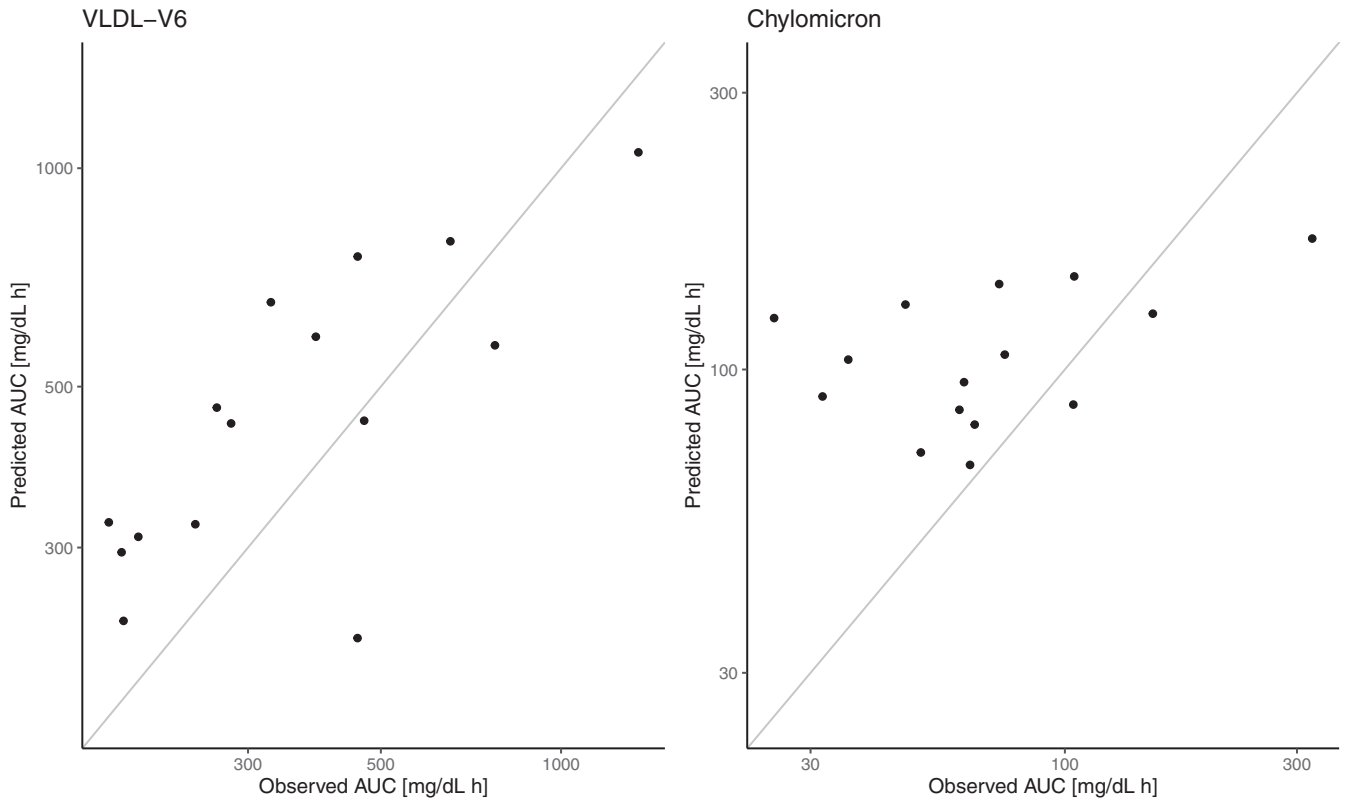

FIGURE 5 Observed versus extended TIGG model-predicted postprandial iAUC of VLDL-V6 (left) or chylomicron (right). iAUC, incremental area under the concentration curve.

chylomicron and VLDL-V6 provided additional information about the glucose homeostasis in the extended period after a meal compared to total TGs. The extended TIGG model was also able to predict the postprandial TG response in chylomicrons and VLDL-V6 using only the total TGs and could thus be used in studies where only total TGs were collected.

AUTHOR CONTRIBUTIONS

J.L. and M.C.K. wrote the manuscript, and designed and performed the research. J.L. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

J.L. is an employee and minor stockholder in Eli Lilly and Company. M.K. declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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